REMARKS

Applicants respectfully request reconsideration of the present application.

CLAIMS STATUS

Pending claims include a) examined claims 11-14, 17-18, 21-25 and 50-52 and b) withdrawn claims 15-16, 19-20 and 27-49.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 11, 12, 14, 17, 18, 21, 22, 25 and 52 stand rejected as obvious over Mautone (USPN 5,306,483). Applicants respectfully traverse.

A. Legal standard of obviousness

Applicants bring the PTO's attention to *KSR International Co. v. Teleflex Inc.*, 550 U.S._, 82 USPQ2d 1385 (2007), where the Supreme Court emphasized that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit (even if the motivation supporting a combination of references is not expressly present in the references). The Supreme Court also stated, quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning the legal conclusion of obviousness.'"

Applicants respectfully submit that the PTO failed to establish a *prima facie* case of obviousness because the PTO relies on conclusory and factually inaccurate statements in its obviousness analysis.

B. Overview of the PTO's formulation of the rejection

On page 3, lines 3-18, the PTO provides its interpretation of Mautone.

On page 4, lines 1-3, the PTO explicitly admits that "the reference does not provide any motivation to select this specific combination of variables DPPC, cholesteryl palmitate,

and sphingomyelin in the form of a liposome." In view of these admitted deficiencies, the PTO acknowledges that Mautone is not an anticipatory reference.

To remedy these admitted deficiencies of Mautone, the PTO cites sections from *KSR v Teleflex,* 127 S.Ct. 1727, 1740 (2007) on page 4, lines 4-18. According to the PTO, the cited sections from *KSR v Teleflex* provide the reasoning for the following conclusion that the PTO makes in the paragraph bridging pages 4-5:

> "Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients specifically DPPC, cholesteryl palmitate, and sphingomyelin in the form of a liposome from within a prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement".

In sum, Applicants' understanding of the rejection is as follows:

1) In the PTO's opinion, Mautone generic disclosure includes all the elements of the claimed invention although not in a single combination;

2) In the PTO's opinion, *KSR v Teleflex* provides reasoning for selecting elements of the claimed invention from Mautone's generic disclosure to arrive at the claimed invention.

Applicants respectfully submit that the PTO is incorrect in relying on either 1) or 2) in its rejection.

C. Fatal Defects In Mautone

Applicants respectfully submit that besides the deficiencies of Mautone explicitly admitted by the PTO in the paragraph bridging pages 3-4, Mautone has a number of additional deficiencies, which include the following:

1) Mautone's disclosure relates to lipid crystals, which are not liposomes. Thus, Mautone's disclosure regarding administering via inhalation of his lipid crystals cannot be applied to liposomes. Similarly, Mautone's disclosure regarding composition of his lipid crystals cannot be applied to liposomes.

2) Mautone does not teach or suggest cholesterol (CH) lipids, which is an element of all pending claims.

Thus, even if for the argument's sake, the PTO's reasoning formulated on page 4 of the Office Action was correct, the PTO still failed to establish a *prima facie* case of

obviousness. This is a completely independent basis upon which the rejection should be withdrawn.

Applicants provide additional explanation regarding Mautone's additional deficiencies below.

1) Mautone relates to lipid crystals, which are not liposomes

According to the PTO, "Mautone is drawn to drug delivery of pharmaceuticals by aerolizing said drug mammalian lungs," see page 3, lines 3-4. This PTO's statement requires clarification because Mautone in fact relates to a specific type of phospholipid delivery system based on a lipid crystal or a lipid crystalline figure, see e.g. abstract; column 3, lines 44-52; column 5, lines 6-8, 49-55. Applicants respectfully submit that Mautone's phospholipid delivery system is not a liposome. Mautone prepares his lipid crystals as follows:

> "(a) preparing a mixture one or more lipids of the group of phospholipids known as phosphatidycholines and one or more spreading agents, in powder form, and said therapeutically active substance and one or more fluorocarbon propellants, said lipids, spreading agents and therapeutically active substance being insoluble in the propellants; and
>
> (b) evaporating the propellants from the mixture," see e.g. column 5, lines 8-16.

The key property of Mautone's lipid crystals is their ability to form a spread film on air/liquid surfaces, see e.g. column 3, lines 44-48; column 5, lines 36-42; column 6, lines 3-9. Mautone mentions the following uses for his lipid crystals:

i) for administering his lipid crystals suspended in a fluorocarbon propellant using a nebulizer, see column 3, lines 48-57; column 5, lines 30-36; column 10, line 63, column 11, line 13. In such a case, the lipid crystals are deposited on an aqueous surface, such as an aqueous lung surface, in the crystalline form, on which surface the lipid crystals form an amorphous surface film utilizing their ability to form spread film, see column 3, lines 52-61, column 5, lines 36-42, column 10, line 63, column 11, line 13. Mautone's examples I-IV relate to lipid crystal suspensions for administering via a nebulizer.

ii) for preparing artificial tears from his lipid crystals. In this application, lipid crystals do not contain drugs. For preparing artificial tears, according to Mautone, the lipid crystals have to be solubulized in propylene glycol, after the propellants have evaporated, see

column 7, lines 40-43. According to Mautone, because "of the hydrophobic nature of the lipids, the use of propylene glycol is helpful in effectively suspending the lipid crystals in aqueous ionic, buffered medium required for delivery to the eye", see column 7, lines 43-46. Mautone's example V relates to artificial tears.

iii) for preparing drug delivery system for eyes from his lipid crystals. This application is analogous to the artificial tears, with the only difference that the lipid crystals do contain a therapeutic substance. Mautone's example VI relates to this application.

iv) for delivering drug or therapeutic agent to the dermal, ophthalmic and mucous membrane and tissues such as hair, skin, nose, mouth, rectum, vagina, urethra and throat, see column 10, lines 56-60. Mautone does not provide details on how his lipid crystals can be used for such applications.

Applicants submit that none of Mautone's lipid crystal based delivery systems including Mautone's lipid mixtures with fluorocarbon propellants, Mautone's lipid crystals suspended in fluorocarbon propellants, Mautone's amorphous films formed from his lipid crystals at an aqueous surface, Mautone's artificial tears prepared from his lipid crystals or Mautone's drug delivery systems prepared from his lipid crystals are liposomes, which Mautone defines in column 3, lines 37-40, as follows: "The liposome is essentially a lipid membrane-bound spherical vesicle, analogous to intracellular organelles, which encapsulates and stores in an aqueous phase the drug(s) to be delivered." The only section of Mautone, which mentions the terms "liposome" or "liposomes", is in column 3, lines 23-44. In particular, in column 3, lines 23-37, Mautone discusses prior art effort of using liposomes, while in column 3, lines 37-44, Mautone provides the above cited definition of liposomes and explains their mode of action. Nowhere in his disclosure Mautone mentions that liposomes can be administered by inhalation, including inhalation via a nebulizer. Applicants submit that the fact that Mautone's lipid crystals are very different from liposomes is also supported by their completely different modes of operation. According to Mautone, liposomes act "by adsorption or fusion to the cell surface, whence either the contents may be liberated and enter the cell by a number of transmembrane routes or the entire liposome may enter the cell by endocytosis," column 3, lines 40-44, while Mautone's lipid crystals act by being deposited "on an aqueous surface ... in the crystalline form, which then instantaneously spreads over

the surface as an amorphous surface film carrying with it the therapeutic drug for which it serves as a vehicle," see column 3, lines 57-61.

Because Mautone's lipid crystals are not liposomes, Mautone's disclosure regarding administering via inhalation of his lipid crystals cannot be applied to liposomes. Thus, Mautone does not teach or suggest administering to a subject in need thereof via inhalation a liposomal formulation comprising liposomes as each of the pending claims recite. Moreover, Mautone teaches away from administering liposomes via inhalation by teaching the advantageous properties of his lipid crystals.

Because Mautone's lipid crystals are not liposomes, Mautone's disclosure regarding composition of his lipid crystals cannot be applied to liposomes. Thus, Mautone does not teach or suggest particular liposome components recited in the pending claims.

In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

2) Mautone does not teach or suggest cholesterol (CH) lipids.

In the footnote on page 3 of the Office Action, the PTO asserts that cholesteryl palmilate is interpreted as a cholesterol lipid. Applicants respectfully submit that cholesterol recited in the pending claims is not a cholesteryl ester, such as cholesteryl palmilate. Applicants respectfully submit that Mautone mentions only cholesteryl esters, such as cholesteryl palmilate, in his disclosure. Nowhere in his patent does Mautone disclose cholesterol. Applicants submit that the PTO itself admitted this deficiency of Mautone when formulating the rejection over Mautone and Taylor on page 5, lines 19-20, of the Office Action by stating "Mautone does not teach the elected species cholesterol, wherein said cholesterol is not an ester." The PTO did not provide reasons on why one ordinary skill in the art would substitute Mautone's cholesteryl ester with cholesterol recited in the pending claims.

In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

D. *KSR v Teleflex* does not permit arbitrary "picking and choosing" of unrelated elements.

The PTO failed to establish a *prima facie* case of obviousness because *KSR v Teleflex* does not provide reasoning for random "picking and choosing" of unrelated elements, which the PTO tries to do in the rejection. Applicants submit that simply quoting sections of *KSR v Teleflex* is not sufficient to establish a *prima facie* case of obviousness because *KSR v Teleflex* requires making an obviousness analysis explicit, which means providing articulated reasoning with some rational underpinning for the legal conclusion of obviousness. Applicants respectfully submit that MPEP § 2143 provides clear guidelines with respect to what constitutes a proper obviousness analysis for certain scenarios discussed in *KSR v Teleflex*. Based on the quotation from *KSR v Teleflex* on page 4, lines 4-11, of the Office Action, Applicants' understanding is that the PTO is trying to apply MPEP § 2143's rationale A), which is "combining prior art elements according to known methods to yield predictable results." Regarding this rationale, MPEP § 2143.A states as follows:

> "To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Then, Office personnel **must articulate** the following
>
> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
>
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, **each element merely performs the same function** as it does separately;
>
> (3) a finding that one of ordinary skill in the art would have recognized that **the results of the combination were predictable**; and
>
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness." (Emphasis added).
>
> "If **any of these findings cannot be made, then this rationale cannot be used** to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." (Emphasis added)

Applicants respectfully submit even if for the argument's sake only, the PTO's analysis of Mautone on page 3 was correct, it can at most satisfy only requirement 1. Because the PTO did not articulate its findings regarding requirements 2-4 in the Office Action, the PTO did not provide the required articulated reasoning with some rational underpinning.

Thus, the PTO failed to establish a *prima facie* case of obviousness. With respect to requirement 3, Applicants emphasize that the present application relates to pharmaceutical arts, which are generally considered to be unpredictable.

In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

Claims 11-14, 17, 18, 21, 22, 24, 25 and 52 stand rejected as obvious over Mautone (USPN 5,306,483) in view of Taylor et al. (Thorax, vol. 47, 1992, p. 257-259). Applicants respectfully traverse.

The PTO failed to establish a *prima facie* case of obviousness because the PTO relies on conclusory and factually inaccurate statements in its obviousness analysis.

In the present rejection, the PTO summarizes its earlier interpretation of Mautone as follows: "Mautone teaches a method of pulmonary administration of a drug comprising administering a liposome comprising DPPC, cholesteryl esters, and sphingomyelin."

As Applicants explained above, the PTO's interpretation of Mautone is factually inaccurate because Mautone does not teach pulmonary administration of liposomes. Instead, Mautone relates to lipid crystal based delivery systems, which are quite different from liposomes. Furthermore, Mautone does not teach a combination of DPPC, cholesteryl esters, and sphingomyelin asserted by the PTO. Applicants submit that arriving at such a combination, which is still different than a combination of DPPC, cholesterol, and sphingomyelin recited in the pending claims, would require picking and choosing of random elements recited in Mautone.

Besides Mautone's deficiencies discussed in the previous paragraph, Mautone has the following additional deficiencies, which the PTO explicitly acknowledges on page 5, lines 19-20:
"Mautone does not teach the elected species of cholesterol, wherein said cholesterol is not an ester. Mautone does not teach an air jet nebulizer."

Taylor does not remedy the deficiencies of Mautone. Although Taylor discloses in the left column, page 258 that a "Hudson jet nebulizer was used to produce aerosols (MMAD 2.6 μm) from a dipalmitoylphosphatidylcholine-cholesterol liposome formulation of sodium cromoglycate", such disclosure is not sufficient to cure the deficiencies of Mautone. One of ordinary skill in the art would not rely on Taylor to cure the deficiencies of Mautone (and vice versa) at least because Mautone and Taylor relate to two completely different systems (lipid crystal based delivery systems in Mautone and liposomes in Taylor), which act by completely different mechanisms. A person of ordinary skill would not select elements from these different delivery systems and put them together.

In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

Claim 23 stands rejected as obvious over Mautone (USPN 5,306,483) in view of Taylor et al. (Thorax, vol. 47, 1992, p. 257-259) and further in view of Mihalko (USPN 5,340,587). Applicants respectfully traverse.

Mihalko does not remedy the discussed above deficiencies of Mautone and Taylor. Thus, because the PTO failed to establish a *prima* facie case of obviousness, Applicants request withdrawal of the rejection.

Claims 50 and 51 stands rejected as obvious over Mautone (USPN 5,306,483) in view of Taylor et al. (Thorax, vol. 47, 1992, p. 257-259) and further in view of Max (European Journal of Pediatrics, Vol. 158, Suppl. 1, 1999, pp. S23-S26). Applicants respectfully traverse.

Max does not remedy the discussed above deficiencies of Mautone and Taylor. Thus, because the PTO failed to establish a *prima* facie case of obviousness, Applicants request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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